Adipose tissue is now regarded as an active endocrine organ which can secrete various cytokines. Adipocyte-derived cytokines are termed adipocytokines (adipocytes + cytokine). Adipocytokines can affect vascular systems to prevent or exacerbate obesity-related vascular complications, including diabetes-related vascular dysfunction, hypertension, and atherosclerosis. However, their basic vascular functions remain to be fully determined. In this manuscript, I summarize our recent findings on the vascular effects of 5 newly identified adipocytokines (omentin, visfatin, nesfatin, vaspin, and chemerin), with a special focus on 1) vascular contractile reactivity, and 2) vascular inflammatory response/injury. These novel adipocytokines may be important future targets for the development of drugs and therapy for treating metabolic vascular disorders.

Key words adipocytokine; contractile reactivity; inflammation; blood vessel; endothelial cell; smooth muscle cell

1. EFFECTS OF NOVEL ADIPOCYTOKINES ON VASCULAR CONTRACTILE REACTIVITY

Previous studies have shown that adipocytokines can potentially affect the contractile reactivity of isolated blood vessels. For example, adiponectin induces nitric oxide (NO)-mediated endothelium-dependent vasodilation in isolated blood vessels.1,2 Similarly, leptin was shown to induce NO-dependent endothelium-dependent vasodilation in isolated blood vessels.3 In contrast, resistin alone had no effects on the contractility of isolated blood vessels, while it specifically inhibits the insulin-mediated endothelium-dependent relaxation.4 Being overweight and/or obese is related to cardiovascular disorders such as hypertension.5 Therefore, it is highly likely that novel adipocytokines might participate in the control of blood pressure by directly acting on the contractile reactivity of blood vessels. Here, I have summarized our recent results on the effects of novel adipocytokines on vascular contractile reactivity.

(1) Effects of Omentin on Contractility of Isolated Blood Vessels Omentin is a novel 313 amino acid adipocytokine originally identified in an omental fat cDNA library in 2005.5,6 It was demonstrated that omentin stimulates insulin-mediated glucose transport in human adipocytes.7 Omentin is more highly expressed in visceral adipose tissues than in subcutaneous adipose tissues.8 The blood concentration of omentin is decreased in overweight and obese human sub-
jects,8) while it increases after obese subjects lose weight.9) Omentin is also known as an endothelial lectin HL-1,10) an intestinal lactoferrin receptor that is expressed in the small intestine of neonates,11) and intelectin-1 that is expressed in the intestinal paneth cells.12,13) We have examined the effects of omentin on the contraction of rat isolated blood vessels. We found that pretreatment with omentin inhibited noradrenaline (NA)-induced concentration-dependent contractions in rat aorta. It was also found in aorta and mesenteric artery that omentin directly induces an endothelium-dependent vasorelaxation, which is mediated by endothelium-produced NO. Omentin-induced NO production was determined to be dependent on the activation of endothelial NO synthase (eNOS) but not phosphatidylinositol 3-kinase (PI3K)/Akt and tyrosine kinase.14) These results might at least in part explain the relationships between obesity and cardiovascular disorders such as hypertension.

(2) Effects of Visfatin on Contractility of Isolated Blood Vessels Visfatin is a novel adipocytokine identified in 2005.15) Although it was originally demonstrated that visfatin exerts insulin-like activities that included a glucose lowering effect by stimulating insulin receptors,16) the biologic effects of visfatin seem to be mediated via an insulin receptor-independent mode based on recent reports.16,17) It was originally shown that blood visfatin levels increase in obese individuals with visceral fat accumulation.18) It was also demonstrated that exercise training with weight loss reduced blood visfatin concentrations.18) However, it was reported by Pagano et al. that blood visfatin concentrations in obese human subjects were somewhat lower than in healthy subjects.19) Visfatin is also known to be a pre-B-cell colony-enhancing factor20) and stimulates B-cell differentiation. We have examined the effects of visfatin on the contractility of rat isolated blood vessels. We found that pretreatment with visfatin inhibited NA-induced concentration-dependent contractions in rat aorta. It was further found in aorta and mesenteric artery that visfatin directly induces an endothelium-dependent vasorelaxation, which is mediated by endothelium-produced NO. Visfatin-induced NO production was determined to be dependent on the activation of PI3K/Akt/eNOS pathways but not insulin receptors.21)

(3) Effects of Nesfatin-1 on Contractility of Isolated Blood Vessels Nesfatin-1 is a nucleobindin 2 (NUCB2)-derived peptide which was originally identified in hypothalamus in 2006.22) Nesfatin-1 expression was recently (2010) identified in mouse and human adipocytes,23) suggesting that nesfatin-1 is also a novel adipocytokine. The expression of nesfatin-1 seems to be increased in mice fed a high fat diet, and blood nesfatin-1 levels show a positive correlation with body mass index (BMI) in humans.23) Nesfatin-1 is thought to be an anorexigenic hormone since intracerebroventricular injection of nesfatin-1 to rats or intraperitoneal application to mice was found to reduce food and water intake24,25) via the activation of melanocortin-3/4 receptors in hypothalamus.22) Moreover, Yosten et al. have recently demonstrated that intracerebroventricular administration of nesfatin-1 caused an increase in mean arterial blood pressure in rats, presumably via the activation of sympathetic nerves through melanocortin-3/4 receptors.26) It was further demonstrated that the hypertensive effects of nesfatin-1 could be prevented by an inhibitor of the hypothalamus oxytocin receptor.26) While it is likely that nesfatin-1 could also affect the vascular contractile reactivity of isolated blood vessels to participate in the control of blood pressure, this still remains to be determined. We have examined the effects of nesfatin-1 on the contractility of rat isolated blood vessels. We observed that nesfatin-1 alone treatment might have no effects on the basal contractility of rat aorta and mesenteric artery. It was also observed that pretreatment with nesfatin-1 had almost no effects on contractile agonist-induced vascular reactivity (Yamawaki and Takahashi, unpublished observation). Further studies are necessary to determine the effects of nesfatin-1 on relaxing agonist-induced vascular reactivity as well as in vivo blood pressure when it is peripherally applied.

2. EFFECTS OF NOVEL ADIPOCYTOKINES ON VASCULAR INFLAMMATORY RESPONSES

It is known that obesity is a risk factor for atherosclerosis.27,28) Vascular endothelial and smooth muscle inflammatory response/injury is one of the early pathogenic features of atherosclerosis.29—31) Previous studies have shown that adipocytokines could potentially affect the vascular inflammatory state. For example, TNF-α is the most well-known pro-inflammatory cytokine and is responsible for various vascular diseases, including atherosclerosis.29—31) In contrast, adiponectin is an anti-inflammatory adipocytokine which protects against vascular diseases.32) We have recently examined whether or not novel adipocytokines are pro-inflammatory or anti-inflammatory in vascular cells. The following is a summary of our recent findings.

(1) Effects of Omentin on Vascular Endothelial Inflammatory Responses Since blood omentin concentrations are reported to be decreased in obese patients (see above), it is likely that omentin could play a role in the prevention or progression of atherosclerosis through its action on the vascular endothelial inflammatory state. We examined the effects of omentin on TNF-α-induced inflammatory responses in human umbilical vein endothelial cells (HUVECs) and observed that omentin could cause NO production via 5′-AMP-activated protein kinase (AMPK)-mediated eNOS phosphorylation, and that omentin-derived NO could inhibit TNF-α-mediated cyclo-oxygenase-2 induction via suppression of c-Jun N-terminal kinase (JNK) activation. Moreover, the omentin-activated AMPK could directly inhibit the p38-mediated e-selectin induction and subsequent lymphocyte adhesion to vascular endothelial cells (Yamawaki and Kuramoto, unpublished observation). These results might at least in part explain the relationships between obesity and cardiovascular disorders such as atherosclerosis.

(2) Effects of Vaspin on Vascular Inflammatory Responses Vaspin (visceral adipose tissue-derived serine protease inhibitor) is a novel 392—395 amino acid adipocytokine identified in 2005 and is a member of the serine protease inhibitor family.33) It was originally discovered in visceral white adipose tissues of Otsuka Long-Evans Tokushima fatty (OLETF) rats, an animal model of type 2 diabetes with obesity.33) Administration of vaspin to obese mice fed a high fat and high sucrose diet improved glucose tolerance and insulin sensitivity.33) It also inhibited the expressions of pro-inflammatory adipocytokines including leptin, resistin, and TNF-α in mesenteric and subdermal white adipose tissues,
suggesting that vaspin might exert an anti-inflammatory role. The blood vaspin concentration in OLETF rats increases at the peak of obesity, body weight, and insulin resistance, whereas it decreases with the worsening of the diabetes. In humans, the blood vaspin concentration in overweight and/or obese subjects is increased compared with lean subjects.\(^{44}\) It was also demonstrated that the blood vaspin level was higher in both non-obese and obese type 2 diabetic patients.\(^{35}\) We have examined the effects of vaspin on basal and TNF-α-induced inflammatory responses in HUVECs. We found that vaspin has almost no effects on the basal endothelial inflammatory responses in HUVECs. We have examined the effects of chemerin on vascular endothelial inflammation. We observed in HUVECs that vaspin may have no effects on basal inflammatory state, but could inhibit TNF-α-induced expression of an adhesion molecule and subsequent lymphocyte adhesion through the suppression of oxidative stress-dependent NF-κB activation. Thus, it might be possible that vaspin plays an inhibitory role with respect to the inflammatory state of vascular SMCs (Yamawaki and Phalitakul, unpublished observation).

(3) Effects of Chemerin on Vascular Endothelial Inflammatory Responses Chemerin is a novel 131—137 amino acid adipocytokine identified in 2007.\(^{37—39}\) Increased chemerin expression in adipocytes was demonstrated in mice fed a high fat diet.\(^{39}\) Chemerin is induced during adipocyte differentiation and increases insulin-stimulated glucose uptake in adipocytes.\(^{40}\) In humans, the blood chemerin concentration seems to be associated with several key factors of metabolic syndrome, such as BMI, blood triglycerides, and blood pressure.\(^{37}\) It was demonstrated that blood chemerin concentrations are increased in severely obese patients.\(^{41}\) Chemerin was originally known as a chemoattractant for immune cells such as macrophages and dendritic cells.\(^{42}\) The effects of chemerin are thought to be mediated via a specific receptor, chemokine-like receptor 1 (CMKLR1), which is a G\(_i\) protein-coupled receptor, and its expression is observed in macrophages, dendritic cells, and adipocytes.\(^{37,39,40,42—44}\) In addition, it has been recently reported that CMKLR1 is expressed in vascular endothelial cells and that its expression level is regulated by inflammatory cytokines, including TNF-α, IL-1β, or IL-6.\(^{45}\) Thus, it is likely that chemerin plays a role in the inflammatory state of vascular endothelial cells. We have examined the effects of chemerin on vascular endothelial inflammation. We observed in HUVECs that chemerin may have no effects on basal inflammatory state, but could induce NO production via the activation of PI3K/Akt/εNOS pathways. The chemerin-produced NO seems to exert anti-inflammatory effects since it could inhibit TNF-α-mediated vascular cell adhesion molecule (VCAM)-1 induction and subsequent lymphocyte adhesion via suppression of the activation of p38 and NF-κB signals (Yamawaki and Kameshima, unpublished observation).

(4) Effects of Visfatin on Vascular Endothelial Inflammatory Responses It has been demonstrated that visfatin mediates vascular endothelial inflammation by inducing the expression of adhesion molecules such as VCAM-1 and intercellular adhesion molecule-1 through oxidative stress-dependent NF-κB activation,\(^{46}\) although this is not our own finding. In monocytes, visfatin also seems to mediate inflammatory responses by inducing the pro-inflammatory cytokines TNF-α, IL-1β, and IL-6,\(^{47}\) while it was demonstrated that higher concentrations of visfatin augmented the expression of anti-inflammatory cytokines such as IL-10.\(^{47}\) Other known functions of visfatin on vasculature are as follows: 1) stimulation of endothelial proliferation and capillary tube formation by producing vascular endothelial growth factor and matrix metalloproteinases through the activation of PI3K/Akt and extracellular signal-regulated kinase (ERK) 1/2 signals,\(^{48}\) and 2) stimulation of vascular smooth muscle cell growth through the activation of ERK 1/2 and p38 signals.\(^{47}\)

CONCLUSION

Are These Novel Adipocytokines Good or Bad? (Fig. 2) In conclusion, omentin may be a good adipocytokine since it inhibits vascular inflammation and induces vasodilation. Similarly, vaspin and chemerin may be good adipocytokines since they inhibit vascular inflammatory responses. However, it should be determined whether or not they could induce vasorelaxation or vasoconstriction in isolated blood vessels. In contrast, we cannot ascertain whether nesfatin-1 is a good or bad adipocytokine at this time. Furthermore, we are unsure whether visfatin is a good or bad adipocytokine since it stimulates vascular inflammation but induces vasodilation. Further detailed studies on the vascular functions of these adipocytokines are necessary. Since these novel adipocytokines are promising and important future targets for the development of new drugs and therapies for the treatment of obesity-related metabolic disorders, this field of research will most likely continue to attract widespread attention.

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